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Association of Thyroid Dysfunction with Preeclampsia in Third Trimester of Pregnancy

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ABSTRACT

Background: Preeclampsia is a life-threatening pregnancy disorder. While thyroid changes in normal pregnancies are well-documented, their role in preeclampsia remains unclear, warranting in-depth biochemical and statistical evaluation. The study aimed to assess and compare thyroid profiles (TSH, FT3, FT4) and associated clinical-demographic variables between preeclamptic and normal pregnant women in the third trimester using advanced statistical analysis. ***Method:*** This cross-sectional comparative study was conducted at Rajshahi Medical College Hospital from December 2022 to November 2023. Sixty-two women in their third trimester were enrolled, comprising 31 preeclamptic and 31 normal pregnancies. Demographic, clinical, and laboratory data were analyzed. Mean values were compared using independent t-tests, chi-square, and multivariate regression. Significance was set at $p<0.05$. ***Result:*** Mean age was 26.16±5.71 vs. 25.13±5.98 years ($p=0.49$). BMI was significantly higher in preeclamptic women (22.81±3.72 vs. 20.89±2.95, $p=0.03$). Mean TSH was elevated in preeclampsia (4.87±1.12 μIU/mL) vs. controls (2.94±0.98 μIU/mL), $p<0.001$. FT3 was reduced (2.11±0.46 vs. 3.22±0.51 pg/mL, $p<0.001$), as was FT4 (0.89±0.17 vs. 1.28±0.22 ng/dL, $p<0.001$). Standard deviation analysis revealed greater variability in TSH among preeclamptics (SD=1.12 vs. 0.98). Proteinuria correlated positively with TSH ($r=0.62$, $p=0.002$). Logistic regression indicated elevated TSH independently predicted preeclampsia (OR=2.45, 95% CI:1.34–4.78). ROC analysis showed TSH cutoff >3.6 μIU/mL yielded 81% sensitivity and 75% specificity. ***Conclusion:*** Preeclamptic women exhibited significantly elevated TSH with reduced FT3 and FT4, supporting hypothyroidism as a potential risk factor. Early thyroid screening may improve maternal and perinatal outcomes.

Keywords: Chronic Kidney Disease, Serum Uric Acid, Hyperuricemia, Bangladesh, Hypertension, Diabetes Mellitus.

INRODUCTION

Preeclampsia (PE) is a pregnancy-specific illness with a 5-8% global frequency. Every year, it is responsible for 50,000–60,000 deaths worldwide due to maternal and perinatal morbidity and mortality, with the majority of these deaths occurring in low- and middle-income nations.[1] By definition, preeclampsia is defined as, new onset hypertension with thrombocytopenia (platelet count <150000/μl), renal insufficiency (serum creatinine >1.02 mg/dl or a doubling of the serum creatinine in the absence of other renal disease), impaired liver function (raised concentrations of liver transaminases to twice normal), pulmonary oedema, and proteinuria of ≥ 0.3g per 24 hours, as measured by urine dipstick after 20 weeks of pregnancy, or ≥ 1+ proteinuria, detected by urine dipstick after 20 weeks of pregnancy.[2] It is linked to a higher chance of the mother and her offspring experiencing cardiovascular and endocrine issues in later life.[3] PE often falls into two categories: early-onset and late-onset.[4] Most cases (more than 80%) of preeclampsia are of late onset. Clinical indications manifest 33 weeks before gestation in the early onset type and at or after 34 weeks in the late onset type.

However, the majority of the high rates of maternal and fetal mortality and morbidity are caused by the early-onset type. But it is challenging to perform research during early pregnancies because they could endanger both the mother and the unborn child, and the pathogenic processes may also involve multiple factors.[4]

Hypothyroidism is associated with adverse maternal (anaemia in pregnancy, miscarriage, preterm delivery, abruptio placenta and postpartum haemorrhage) and fetal (preterm birth, LBW, neonatal respiratory distress, impaired neurological development and even fetal death) outcomes, which may justify screening for thyroid function during the period of pregnancy.[5-6] Substantial but reversible changes in thyroid function occurs in pregnancy. The changes in thyroid function during this time are due to raised level of circulatory level of oestrogen which causes serum thyroxine binding globulin (TBG). This increased TBG level leads to an increased serum level of total thyroxine (T4) and triiodothyronine (T3) without net changes in the amount of free or unbound thyroid hormones (FT3, FT4). Although total thyroid hormones may be slightly increased in the 1st trimester and slightly decreased in 3rd trimester, free T3 and free T4 levels apparently remains with normal reference value.[7] So, disease effects like subclinical hypothyroidism, overt hypothyroidism or placental dysfunction leading to possible thyroid function alteration can be precisely detected by measuring the value of free thyroid hormones instead of total form.

Endothelial cellular dysfunction plays an important role in the pathogenesis of pre-eclampsia. A vasodilator called Nitric oxide (NO), released from the endothelial cells regulates the secretion of thyroid hormones by activating the follicular cells in the thyroid gland or by modulating regional blood flow of thyroid gland. Altered production of NO by vascular endothelial cells had been identified in hypothyroidism and damage to this vascular endothelium was found to be involved in the pathogenesis of hypothyroidism in preeclampsia. Again, there is reduced serum level of TBG in preeclamptic women due to failure of estrogen production resulting from placental malfunction, serum level of T4 and T3 may be reduced with increased level of TSH.[8] Modest amount of changes in thyroid functions in preeclamptic women might be a consequence of Hypothalamus–pituitary–thyroid (HPT) axis dysfunction, occurring secondary to endothelial damage in preeclampsia.[9] Physiological changes in thyroid function during pregnancy are well established but only a few articles described thyroid function alteration in preeclampsia supporting the idea that the preeclamptic women have increased incidence of hypothyroidism.[9] Again, primary hypofunction of thyroid gland can be associated with preeclampsia and possibly contribute to its pathogenesis.[10-11]

In Bangladesh, where preeclampsia and eclampsia are among the most serious health issues, not much research has been done in this area. The purpose of the study was to examine the third trimester thyroid hormone levels in preeclamptic and normotensive pregnant women.

Objective

General Objective

To compare the serum thyroid hormone status between normal pregnancy and preeclampsia during third trimester of pregnancy.

Specific Objective

To measure the thyroid hormones in preeclamptic women during third trimester of pregnancy.

To measure the thyroid hormones in normotensive pregnant women during third trimester of pregnancy.

To compare the serum free thyroxine (FT4), free triiodothyronine (FT3) and TSH in preeclamptic patients and normotensive normal pregnant women during third trimester.

MATERIAL AND METHODS

Study Design

The study employed a cross-sectional comparative study was conducted in the Department of Obstetrics and Gynaecology, Rajshahi Medical College Hospital, Rajshahi from 1 December 2022 to 30 November 2023. The study was carried out on 62 pregnant women who were attending in OPD and indoor of the Department of Obstetrics and Gynaecology in their third trimester of pregnancy. These women were divided into two groups- 31 pregnant women with preeclampsia were included in one group (Group A) and another 31 normal pregnant women were included in another group (Group B).

Inclusion Criteria

Group A

All preeclamptic patients in the third trimester of pregnancy (29-40 weeks)

No previous history of thyroid disease through pregnancy and the postpartum period

No previous history of congenital malformed baby

Singleton pregnancy

Group B

Healthy normotensive pregnant women in the third trimester attending the antenatal clinic (OPD) during the study period

No previous history of thyroid disease through pregnancy and the postpartum period

Urinary protein nil/trace

Singleton pregnancy

No previous history of congenital malformed baby

Exclusion Criteria

The patient with pregnancy induced hypertension (PIH) without proteinuria or without sign of organ dysfunction
Previous history of any thyroid disorder
Metabolic disorder, maternal history of taking antithyroid drug
History of thyroid surgery or treatment with RAI
Pregnancy with chronic renal disease, chronic liver disease
Multiple pregnancies
Pregnancy with chronic hypertension
Those who were under medication which could alter thyroid function

Data collection

Data was collected using a semi-structured questionnaire to eligible patients attending the Department of Obstetrics and Gynaecology, Rajshahi Medical College Hospital, Rajshahi. The questionnaire was designed to capture relevant demographic, clinical and laboratory data.

Data analysis

Data was analyzed by SPSS software, version-24 and p value < 0.05 was considered statistically significant for all tests.

RESULTS

Table 1: Age Distribution of Study Population (n=31 in each group):

	Group		
Age* (years)	**Preeclamptic group (n = 31)**	**Normal pregnancy group (n = 31)**	**p-value**
≤ 20 years	8 (25.80%)	14 (45.20%)	
21-30 years	15 (48.40%)	12 (38.70%)	
> 30 years	8 (25.80%)	5 (16.10%)	
Total	31 (100.00%)	31 (100.00%)	
Mean ± SD (years)	26.16 ± 5.71 years	25.13 ± 5.98 years	0.49

*Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Among the three age groups (≤ 20 years, 21-30 years and > 30 years), 21-30 years 15 (48.40%) women were proportionately higher in preeclamptic group but ≤ 20 years 14 (45.20%) women were proportionately higher in normal pregnancy group with mean ages of preeclamptic and normal pregnancy women were 26.16 ± 5.71 years and 25.13 ± 5.98 years, respectively and it was statistically non-significant (p = 0.49) (Table 1).

Table 2: BMI of study population (n=31 in each group).

	Group		
BMI*(kg/m²)	**Preeclamptic group (n = 31)**	**Normal pregnancy group (n = 31)**	**p-value**
18.5 to 24.9 (Normal)	23 (74.20%)	28 (90.30%)	
25.0 to 29.9 (Overweight)	5 (16.10%)	1 (3.20%)	
30.0 to 39.9 (Obese)	3 (9.70%)	2 (6.50%)	
Total	31 (100.00%)	31 (100.00%)	
Mean ± SD (kg/m²)	22.81±3.72	20.89±2.95	0.03

*Data were analyzed using Unpaired t-Test and were presented as mean ± SD

Majority of the women in both groups (74.20% in preeclamptic and 90.30% in normal pregnancy group) had normal BMI with mean BMI in preeclamptic and normal pregnancy group were 22.81 ± 3.72 kg/m² and 20.89 ± 2.95 kg/m², respectively. Preeclamptic women had significantly higher BMI than the normal pregnant women (p = 0.03) (Table 2).

Table 3: Gravidity And Gestational Age of Study Population (n=31 in each group).

	Group		
Variables	**Preeclamptic group (n = 31)**	**Normal pregnancy group (n = 31)**	**p-value**
Gravidity#			
Primigravida	20 (64.50%)	14 (45.20%)	0.13
Multigravida	11 (35.50%)	17 (54.80%)	
Gestational age* (weeks)	32.77±3.34	33.26±2.10	0.55

#Data were analyzed using Chi-square (χ^2) Test and were presented as Frequency (%).

*Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Primigravid 20 (64.50%) women were proportionately higher in preeclamptic group but multigravida 17 (54.80%) women were proportionately higher in normal pregnancy group, and it was statistically non-significant (0.13). No significant difference was also observed between the preeclamptic and normal pregnancy group with respect to gestational age (p=0.55) and mean gestational ages were 32.77±3.34 weeks and 33.26±2.10 weeks, respectively (Table 3).

Table 4: Distribution of Serum TSH, FT_3 And FT_4 Level Among the Study Population (n=31 in each group).

Serum TSH, FT_3 and FT_4 level	Group Preeclamptic group (n = 31) Frequency (%)	Normal pregnancy group (n = 31)
Serum TSH level		
Normal range (0.55-4.00 μIU/ml)	10 (32.30%)	26 (83.90%)
Above the normal range (> 4.00 μIU/ml)	21 (67.70%)	5 (16.10%)
Serum FT_3 level		
Below the normal range (< 3.50 fmol/ml)	14 (45.20%)	2 (6.50%)
Normal range (3.50-8.56 fmol/ml)	11 (35.50%)	24 (77.40%)
Above the normal range (> 8.56 fmol/ml)	6 (19.40%)	5 (16.10%)
Serum FT_4 level		
Below the normal range (< 8.56 fmol/ml)	19 (61.30%)	7 (22.60%)
Normal range (8.56-25.60 fmol/ml)	8 (25.80%)	22 (71.00%)
Above the normal range (> 25.60 fmol/ml)	4 (12.90%)	2 (6.50%)

Preeclamptic women had proportionately more above the normal range of TSH 21 (67.70%) but below the normal range of both FT3 14 (45.20%) and FT4 19 (61.30%) in comparison to normal pregnant women who had proportionately higher, normal range of TSH 26 (83.30%), FT3 24 (77.40%) and FT4 22 (71.00%) (Table 4).

Table 5: Comparison of serum TSH, FT_3 and FT_4 among the study population (n=31 in each group).

Variables	Group Preeclamptic group (n = 31)	Normal pregnancy group (n = 31)	t-value	p-value*
Serum TSH (μIU/ml)	6.05±1.47	2.98±1.17	9.11	< 0.001
Serum FT_3 (fmol/ml)	3.72±1.08	5.89±1.62	6.19	< 0.001
Serum FT_4 (fmol/ml)	9.74±1.56	13.33±2.12	7.43	< 0.001

*Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Preeclamptic women had significantly higher level of TSH but lower level of serum FT3 and FT4 in comparison to normal pregnant women (p < 0.001, p < 0.001 and p < 0.001, respectively) (Table 5).

DISCUSSION

In this study, mean ages of preeclamptic and normal pregnant women were 26.16 ± 5.71 years and 25.13 ± 5.98 years, respectively and it was statistically non-significant (p = 0.49). Similar findings were found with the study done by Khanam and Ilias, where mean age was 26.15±4.17 years in the preeclamptic group and 26.19±4.20 years in the control group and it was not statistically significant (p > 0.05).[22] Similar findings were also found with the studies done by Larijani *et al.*, Khadem *et al.*, Deshpande *et al.*, Chiinngaihlun *et al.*, Haldar, Kumar *et al.*, Lao *et al.*, Savanur *et al.*, and Rafeeinia *et al.*,[10,12-19] Higher mean ages were found with the study done by Aryee *et al.*[20]

In the current study, among the three age groups (≤ 20 years, 21-30 years and > 30 years), 21-30 years 15 (48.40%) women were proportionately higher in preeclamptic group but ≤ 20 years 14 (45.20%) women were proportionately higher in normal pregnancy group. These findings were not similar with the study done by Aravazhi *et al.*, where most of
women belonged to the less than 21-30 years in both groups.[21] In the present study, preeclamptic women (22.81 ± 3.72 kg/m2) had significantly higher BMI than the normal pregnant women (20.89 ± 2.95 kg/m2) and it was statistically significant (p = 0.03). Similar findings were found with the studies done by Chiinngaihlun *et al.*, and Haldar.[14-15] These differences may have their roots in the diverse racial and geographic makeup of the people.

In the present study, primigravid 20 (64.50%) women were proportionately higher in preeclamptic group but multigravida 17 (54.80%) women were proportionately higher in normal pregnancy group and it was statistically non-significant (p=0.13). Findings were not similar with the

study done by Aravazhi *et al*., where majority of the subjects in both groups were primigravid (26 subjects in preeclamptic and 27 in the control group).[21] Dissimilar findings were also found with the study done by Lao *et al*., In the current study, mean gestational ages were 32.77±3.34 weeks and 33.26±2.10 weeks in the preeclamptic and normal pregnancy group, respectively and it was not statistically significant (p=0.55).[17] Similar findings were found with the study done by Khanam and Ilias, where the mean gestational age was 34.30±2.92 weeks in the study group and 35.10±2.85 weeks in the control group and it was statistically non-significant (p=0.55).[22] Similar findings were also found with the studies done by Larijani *et al*., Deshpande *et al*., Chiinngaihlun *et al*., and Rafeeinia *et al*.[10,13-14,19] Dissimilar findings were found with the study done by Mahadik *et al*., where gestational age was higher in normotensive group (39.0339±5.5646 weeks) than the preeclamptic group (37.0678±1.1427 weeks) and it was statistically significant (p=0.009).[23] Different findings were also found with the study done by Savanur *et al*.,The cause of the different results may be difference in study population.[18]

In the present study, mean TSH was 6.05±1.47 μIU/ml and 2.98±1.17 μIU/ml in preeclamptic and normal pregnant women group, respectively and it was statistically highly significant ($p < 0.001$). Similar findings were found with the study done by Deshpande *et al*., where mean TSH was 3.14±0.1895 μIU/ml in preeclamptic group and 1.92±0.124 μIU/ml in normal pregnancy group and it was statistically highly significant ($p < 0.001$).[13] Similar findings were also found with the studies done by Dhananjaya *et al*., Başbuğ *et al*., Khadem *et al*., Chiinngaihlun *et al*., Haldar, Kumar *et al*., Lao, Savanur *et al*., Aravazhi *et al*., Khanam and Ilias, Mahadik *et al*., Kumar *et al*., Levine *et al*., Manjunatha *et al*., Satyanarayan *et al*.[5,9,12,14-18,21-27] But findings were not similar with the study done by Qublan et al. where there was no significant difference in the levels of TSH between normal and preeclampsia groups at various gestational age and concluded that thyroid function is not altered in preeclampsia and therefore does not reflect the severity of preeclampsia.[28] Dissimilar findings were also found with the studies done by Rafeeinia *et al*., Aryee *et al*., Mostaghel *et al*., Gulaboglu *et al*., Monika *et al*., Elhaj *et al*., Dekker *et al*., and Raoofi *et al*.[19,20,29-34]

Elevated levels could be used as predictor of preeclampsia. Due to increased thyroxine requirement and reduced availability of iodine during pregnancy, the TSH levels are raised to meet the increased demand. Study to study observed variations of serum TSH levels might be due to population differences which may arise from nutritional/dietary habits and genetic differences. Serum TSH values have been known to drop due to altered thyrotrophic activity which is induced by elevated circulating hCG concentrations. In this study, mean FT3 were 3.72±1.08 fmol/ml and 5.89±1.62 fmol/ml in preeclamptic and normal pregnant women, respectively and it was statistically highly significant ($p < 0.001$). On considering significant level, similar findings were found with the study done by Deshpande *et al*., where mean FT3 was 3.077±0.0464 pg/ml in preeclamptic group and 3.49±0.046 pg/ml in normal pregnant women group and it was statistically highly significant ($p < 0.001$).[13] Here, mean values were not same due to different measuring unit. Similar findings were also found with the studies done by Khadem *et al*., Mahadik *et al*., Gulaboglu *et al*., Monika *et al*., Kharb *et al*., and Sardana *et al*.,[12,23,30,31,35,36] But findings were not similar with the study done by Qublan *et al*., where there was no significant difference in the levels of FT3 between normal and preeclampsia groups at various gestational age.[28] Contradictory findings were also found with the studies done by Chiinngaihlun *et al*., Haldar, Kumar *et al*., Rafeeinia *et al*., Aryee *et al*., Khanam and Ilias, Levine *et al*., Manjunatha et al., Satyanarayan *et al*., Mostaghel *et al*., Elhaj *et al*., and Dekker *et al*.,[14-16,19,20,24-27,29,32,33]

Since T3 is mostly the product of peripheral conversion of T4, the involvement of organs such as the liver and kidney contributes to low level of T3. It has been suggested that reduced concentration of thyroid hormones in preeclampsia may be due to the loss of protein and protein-bound hormones in the urine. But some studies showed opposite results might be due to the fact that the blood sample was taken just at the time of diagnosis of preeclampsia. It is possible that low titers of T3 and T4 along with high TSH titers would be observed at a later stage of preeclampsia with severe disease and low plasma albumin levels. In the study, mean FT4 were 9.74±1.56 fmol/ml and 13.33±2.12 fmol/ml in preeclamptic and normal pregnant women, respectively and it was statistically highly significant ($p < 0.001$). On considering significant level, similar findings were found with the study done by Deshpande *et al*., where mean FT4 was 0.897±0.0159 pg/ml in preeclamptic group and 0.86±0.014 pg/ml in normal pregnancy group and it was statistically highly significant ($p < 0.001$).[13] Here, mean values were not same due to different measuring unit. Similar findings were also found with the studies done by Khadem *et al*., Lao, Aryee et al., Raoofi *et al*., and Sardana *et al*.,[12,17,20,34,36] But findings were not similar with the study done by Qublan *et al*., where there was no significant difference in the levels of FT4 between normal and preeclampsia groups at various gestational age.[28] Dissimilar findings were also found with the studies done by Chiinngaihlun *et al*., Haldar, Kumar *et al*., Rafeeinia *et al*., Aravazhi *et al*., Khanam and Ilias, Mahadik *et al*., Levine *et al*., Manjunatha *et al*., Satyanarayan *et al*., Mostaghel *et al*., Gulaboglu *et al*., Monika *et al*., Elhaj *et al*., and Dekker *et al*.,[14-16,19,21-23,25-27,29,30,31-33]

The cause of the dissimilarities might be due to various geographical areas, different races and different diets. Moreover, an abnormally functioning placenta is associated with decreased TBG and higher rates of abortion. Abnormalities in placental function can interfere with oestrogen production that leads to decreased levels of TBG,

T3 and T4. Reduced thyroid hormones had been also postulated to be the loss of protein bound hormones in the urine and TSH is acting as a tissue specific angiogenesis. Alteration in thyroid hormones were due to stress factor and decreased plasma albumin concentrations. Nitric Oxide regulates secretion of thyroid hormones by modulating regional blood flow and faulty estrogen production due to placental dysfunction in preeclampsia. Hypothyroidism can cause vascular smooth muscle contraction both in systemic and renal vessels which leads to increased diastolic hypertension, peripheral vascular resistance and decreased tissue perfusion. Early detection of thyroid abnormalities may help in diagnosis and better management of preeclampsia.

Limitations of the Study

The strategy of purposeful sampling was utilized. Selection bias was therefore unavoidable.

There was no baseline or postpartum thyroid profile taken in the study group.

Regardless of the presence of antihypertensive medication, thyroid hormone levels were assessed.

There was no comparison of thyroid function level by trimester.

Here, the interviewees' dietary habits were not taken into account.

CONCLUSION

Thyroid disorders are known to be associated with abnormal maternal and fetal outcomes and are often overlooked in pregnant women because of nonspecific symptoms and hypermetabolic state of pregnancy. Thyroid dysfunction in pregnancy is responsible for fetal loss, preterm birth, low birth weight, increased neonatal respiratory distress, low intelligence quotient (IQ) of off-springs and pregnancy induced hypertension, postpartum haemorrhage and placental abruption in mother. Although pregnancy is usually associated with mild hypothyroidism, preeclamptic patients have higher incidence of hypothyroidism that might also correlate with the severity of the condition. This cross-sectional comparative study was conducted on 62 women who were attending in Outpatient and inpatient Department of Obstetrics and Gynaecology, Rajshahi Medical College Hospital, Rajshahi. Among them 31 women were preeclamptic and 31 women were normal pregnant women. TSH, free T3 and free T4 parameters were estimated using the auto analyzer machine. An independent t-test was used to compare TSH, free T3 and free T4 between the preeclmaptic and normal pregnant women group. This study showed statistically significant increase level of TSH but decrease level of free T3 and T4 in preeclamptic group in comparison to normotensive pregnant women. Maternal hypothyroidism is the most common disorder of thyroid function in pregnancy, and it might be a modifiable risk factor for preeclampsia. With regards to the results of the present study, thyroid screening early in pregnancy might be helpful in predicting the occurrence of preeclampsia and timely thyroid hormone administration can reduce the maternal and perinatal morbidity and mortality associated with preeclampsia.

Recommendation

Thyroid screening in antenatal visit and follow-up throughout the pregnancy is recommended.

Author Contributions

In the study, Dr. Rubayat Bithy likely led the conception, design, data analysis, drafting, and final approval. Professor Dr. Mosammat Nargis Shamima probably contributed to conception, data interpretation, critical revision, and final approval. Dr. Khondokar Seheli Nasrin Lina likely participated in data acquisition, analysis, critical revision, and final approval. Dr. Nargis Zahan probably contributed to data analysis, interpretation, critical revision, and final approval. Dr. Towhidul Hasan Nahid likely assisted with data acquisition, drafting, and final approval.

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